REMARKS

Claims 1-16 are canceled, claims 17-22 were pending, Claim 18 is withdrawn from consideration. Claim 17 is amended. New claim 23 is added.

Support for the amending language "normalized to be a ratio of test to control data on the same cell type under control conditions" may be found in the specification at paragraph 49. Support for the amending language "analyzing said biomap by a multiparameter pattern recognition algorithm to quantify relatedness of said biomap to reference biomaps" may be found in the specification at, *inter alia*, paragraphs 5, 53, 79, 134 and 139. Applicants note that Example 4, "Analysis in Multiplex Assay Combinations for Identifying Mechanism of Action" is relevant to such language.

Claim 17 has been rejected under 35 U.S.C. 112, second paragraph. The Office Action states that the term "amount sufficient" is a relative term that renders the claim indefinite. Without conceding to the correctness of the rejection, Claim 17 has been amended to recite that "a plurality of pathways are induced by the presence of the factors", thereby deleting the relative term. In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 17 and 19-22 have been rejected under 35 U.S.C. 102(e) as anticipated by Friend et al., U.S. Patent no. 6,801,859.

Applicants respectfully submit that the presently claimed invention is not anticipated by the cited reference. The invention of the present claims, as set forth in independent Claim 17, recites the step of contacting a mammalian cell culture with a compound to be characterized, where the cells in the culture have a plurality of signaling pathways activated by at least two factors. The cited reference describes methods for screening molecules using cell co-cultures, wherein the cell cultures differ by expression of a single target gene by over- or under-expression. The methods do not employ a cell culture comprising at least two factors or in which a plurality of pathways are activated.

As stated by Friend *et al.*, in the summary of the invention, the prior art patent provides methods for determining "a consensus profile for a biological response, such as the response of an organism to a group or family of drugs and/or drug candidates."

It is stated that "The methods of the present invention include: (i) obtaining or providing response profiles for the biological response (or responses) of interest; (ii) defining sets of co-

regulated cellular constituents (i.e., genesets) in the response profiles; and (iii) identifying common response motifs among the defined sets of co-regulated cellular constituents which are associated with particular biological responses such as drug effectiveness or toxicity. The common response motifs thereby identified comprise the consensus profiles of the invention."

In particular, in the overview of the methods of the invention (column 10), it is stated that:

> The methods of the invention analyze response profiles which are obtained or provided (101) from measurements of aspects of the biological state of a cell in response to a particular set or sets of perturbations, such as drug exposure, targeted mutations, or targeted changes in protein activity or expression. Specifically, aspects of the biological state of a cell, for example, the transcriptional state, the translational state, or the activity state, are measured in response to a plurality perturbations. Preferably, the measurements are differential measurements of the change in cellular constituents in response to the drug at certain concentrations and times of treatment. The collection of these measurements, optionally graphically presented, are called herein the "perturbation response" or "drug response" or "response profile." Preferably, a plurality of drug response profiles are obtained or provided for a plurality of different drugs, specifically for those drugs for which a consensus profile is desired (e.g., for each member of a particular class or family of drugs, or for perturbations in the expression and or activity of primary targets of those drugs). However, response profiles may also be obtained or provided for other drugs or conditions, such as genetic mutations, which are associated with a particular biological effect or effects of interest. In most embodiments, at least five, preferably more than ten, more preferably more than 50, and more preferably more than 100 different perturbations are employed.

From the above description, one of skill in the art is informed that the methods of the prior art involve perturbing a cell culture with drug exposure, targeted mutations, or targeted changes in protein activity or expression, and measuring the transcriptional state, the translational state or the activity state. From these data a set of responses is developed for further analysis, and grouped according to their similarities.

In the methods of the present invention, a test agent contacts cells in culture that are stimulated in multiple pathways by the addition of at least two factors. Applicants respectfully submit that there is no teaching by Friend *et al.* that would inform one of skill in the art perform such analysis in the presence of at least two factors acting on the cell.

Applicants have observed that the activation of cells in multiple pathways reveals properties of test agents that are cryptic in the absence of these factors. Many biologically active agents were found to have no detectable change in parameters when brought into contact with unstimulated cells. Yet when added to cells stimulated in multiple pathways, as in the methods of the invention, distinctive parameter changes could be observed.

For example, as shown in Table 1, the compounds AA861, SB 203580, PD098059, and AG126 can be added to a culture of unstimulated HUVEC cells, and after 24 hours the parameter read-outs for ICAM-1, VCAM-1, E-selectin, IL-8, CD31, HLA-DR and MIG would be indistinguishable from controls lacking the agents; and thus would be indistinguishable from each other. Yet, when

applied to stimulated cells each of these agents generated a distinctive profile typical of the mechanism of action, *i.e.* NF□B signaling pathway vs. p38 MAPK pathway vs. P42/44 MAPK signaling pathway, *etc.*

The Office Action asserts that Friend et al. teaches, at column 6, lines 43-46 and column 52, lines 23-25 a culture comprising a plurality of factors in an amount sufficient to induce a plurality of pathways.

The cited paragraph at column 6 reads as follows:

> According to the current invention, drugs are any compounds of any degree of complexity that perturb a biological system, whether by known or unknown mechanisms and whether or not they are used therapeutically. Drugs thus include: typical small molecules of research or therapeutic interest; naturally-occurring factors, such as endocrine, Paracrine, or autocrine factors or factors interacting with cell receptors of all types; intracellular factors, such as elements of intracellular signaling pathways; factors isolated from other natural sources; pesticides; herbicides; insecticides; and so forth. The biological effect of a drug may be a consequence of, inter alia, drug-mediated changes in the rate of transcription or degradation of one or more species of RNA, the rate or extent of translation or post-translational processing of one or more polypeptides, the rate or extent of the degradation of one or more proteins, the inhibition or stimulation of the action or activity of one or more proteins, and so forth. In fact, most drugs exert their effects by interacting with a protein. Drugs that increase rates or stimulate activities or levels of a protein are called herein "activating drugs", while drugs that decrease rates or inhibit activities or levels of a protein are called herein "inhibiting drugs". As will be clear to the skilled artisan, while the invention is described herein in terms of determining a consensus profile for different drugs, and using them to identify the activity of a "drug," it is equally applicable to determining a consensus profile for different preparations of a particular drug, i.e., compositions which comprise or contain a particular drug but also contain different additional ingredients.

And the cited paragraph at column 52 reads as follows:

> An exemplary display is illustrated in FIGS. 2 and 3. Specifically, FIG. 2A shows a gray scale display of a plurality of genetic transcripts (horizontal axis) measured in a plurality of experiments (vertical axis), i.e., response profiles, wherein cells are exposed to different perturbations (e.g., graded exposure to different drugs). Thus, each row in FIG. 2A indicates the response of genetic transcripts to a particular perturbation (e.g., exposure to a particular drug). Black denotes up regulation of a transcript (+1), whereas white denotes down regulation (-1), and the middle gray scale (0) denotes no change in expression. FIG. 2B illustrates the grouping of genetic transcripts into genesets by means of a coregulation tree (described in Section 5.3.3 below), and FIG. 2C illustrates the visual display of the re-ordered transcripts. FIG. 2D illustrates the visual display of both re-ordered transcripts and re-ordered profiles.

Applicants respectfully submit that the cited sections of Friend *et al.* do not teach a method of analysis wherein an agent contacts a mammalian cell culture, wherein said culture comprises a plurality of factors and wherein a plurality of pathways are induced by the presence of the factors. The cited paragraph from column 6 teaches that drugs have different biological effects and can be inhibitory or activating. The paragraph from column 52 teaches the scale by which different

responses are illustrated in the prior art figures. It is not seen how these sections, when properly read in their entirety, could be interpreted as teaching cell cultures activated by multiple factors.

In discussing drug action, Friend defines drugs as including "typical small molecules, naturally occurring factors, . . . pesticides, etc." Column 6, lines 42-47. Such a use is distinct from the presently claimed methods. In the subject methods, the biological state of interest in an *in vitro* culture (in the absence of test drug) contains a plurality of factors that induce a plurality of pathways (separate from the issue of what the drug or test agent is).

In the methods of Friend, therefore, a drug, which may be a factor, is introduced into a cell culture, usually a yeast cell culture, as a single active agent. In contrast, in the methods of the present invention, a culture of mammalian cells is activated in a plurality of signaling pathways, and the effect of an agent on those activated cells is compared to the activated cells in the absence of the agent.

Applicants respectfully submit that the cited art fails to teach every element of the claimed invention. In view of the above remarks, withdrawal of the rejection under 35 U.S.C. 102 is requested.

Claims 17 and 19-22 have been rejected under the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-16 of U.S. Patent no. 6,656,695. Applicants agree to the filing of a terminal disclaimer upon indication of patentable subject matter.

Claims 17 and 19-21 have been provisionally rejected on the ground of nonstatutory obviousness type double patenting as being unpatentable over Claims 1, 7, 9, 10, 14, 33, 34 and 35 of co-pending application no. 10/220,999.

Applicants respectfully submit, as set forth in MPEP 804,

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.
> If the "provisional" double patenting rejections in both applications are the only rejections remaining in those applications, the examiner should then withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent. The examiner should maintain the double patenting rejection in the other application as a "provisional" double patenting

rejection which will be converted into a double patenting rejection when the one application issues as a patent.

Therefore, it is proper to allow the present application to issue, thereby converting the provisional rejection to a double patenting rejection.

CONCLUSION

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number SEEK-001CON.

Respectfully submitted,

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